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09/634,252		Douglas P. Cerretti	03260.0051	3642

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/634,252	Applicant(s) CERRETTI, DOUGLAS P.	
	Examiner William W. Moore	Art Unit 1652	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-29* is/are pending in the application.

4a) Of the above claim(s) *19,20,24 and 26-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,21-23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *15-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment

Applicant's Preliminary Amendment, Paper No.2 filed with the application on August 7, 2000, has been entered, amending pages 1 and 6 of the specification, canceling the original claims 1014 and adding the new claims 15-29.

Drawings and Information Disclosure Statement

The Drawing Figures 1 and 2 filed with the application on August 7, 2000, have been APPROVED by the Draftsperson. Applicant's Information Disclosure Statement, Paper No. 3 filed December 12, 2000, has been entered and documents cited therein are made of record with the PTO Forms-1449 that accompany this communication.

Election/Restrictions

Restriction is required under 35 U.S.C. §§121 and 372.

This application contains the following inventions or grou ps of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

I. Claims 15-18 and 21-23, drawn to a first polynucleotide product of SEQ ID NO:1, to a corresponding first polypeptide product of SEQ ID NO:3, to vectors and host cells comprising the polynucleotide, and to a first method of use of the polynucleotide in recombinant expression of the polypeptide in a host cell, classified under national practice in, *inter alia*, class 536, subclass 23.2.

II. Claims 15-18, 21-23 and 25, drawn to a second polynucleotide product of SEQ ID NO:2, to a corresponding second polypeptide product of SEQ ID NO:4, to vectors and host cells comprising the polynucleotide, and to a first method of use of the polynucleotide in recombinant expression of the polypeptide in a host cell, classified under national practice in, *inter alia*, class 536, subclass 23.2

III. Claims 15-18 and 21-24, drawn to a third polynucleotide product of SEQ ID NO:5, to a corresponding third polypeptide product of SEQ ID NO:6, to vectors and host cells comprising the polynucleotide, as well as to a first method of us of the polynucleotide in recombinant expression of the polypeptide in a host cell, classified under national practice in, *inter alia*, class 536, subclass 23.2.

IV. Claims 15-18, 21-23 and 25, drawn to a fourth polynucleotide product, which may be chimeric, comprising a region encoding one of several species of domains of the polypeptide product of SEQ ID NO:4, to vectors and host cells comprising the polynucleotide, and to a first method of use of the polynucleotide

in recombinant expression of the polypeptide in a host cell, classified under national practice in, *inter alia*, class 536, subclass 23.2

V. Claims 15-18 and 21-24, drawn to a fifth polynucleotide product, which may be chimeric, comprising a region encoding one of several s pecies of domains of the polypeptide product of SEQ ID NO:6, to vectors and host cells comprising the polynucleotide, and to a first method of use of the polynucleotide in recombinant expression of the polypeptide in a host cell, classified under national practice in, *inter alia*, class 536, subclass 23.2.

VI. Claims 19 and 20, drawn to a first antibody product specific for the amino acid sequence of SEQ ID NO:4, classified under national practice in class 530, subclass 387.1.

VII. Claims 19 and 20, drawn to second antibody product specific for the amino acid sequence of SEQ ID NO:6, classified under national practice in class 530, subclass 387.1.

VIII. Claims 26-28, drawn to a method of use of a polypeptide product of SEQ ID NO:4 in an assay to detect inhibitors, classified under national practice in class 435, subclass 23.

IX. Claims 26-28, drawn to a method of use of a polypeptide product of SEQ ID NO:6 in an assay to detect inhibitors, classified under national practice in class 435, subclass 23.

X. Claim 29, drawn to first method of *de novo* design of an inhibitor based on the three-dimensional structure of the polypeptide product SEQ ID NO:4, classified under national practice in class 702, subclass 19.

XI. Claim 29, drawn to a second method of *de novo* design of an inhibitor based on the three-dimensional structure of the polypeptide product SEQ ID NO:6, classified under national practice in class 702, subclass 19.

Inventions of Groups I-V lack unity of invention, each with the other, becau se as many as five separate and distinct polynucleotide products are described by the claims and each is disclosed to have a special technical feature defined by its coding capacity for a native protease having, respectively, the amino acid sequences of SEQ IDs NOs: 2, 4 and 6, and chimeric polypeptides which need not comprise protease domains of SEQ IDs NOs: 4 and 6, whereby the coding capacity of each corresponding polynucleotide is considered to link it in a single inventive concept to the encoded amino acid sequence of each corresponding protease in the absence of disclosure of a further special technical feature common to any of the native proteases or chimeric polypeptides.

Inventions of Groups I-V lack unity of invention with inventions of Groups VI and VII because polynucleotide products of Group I-V are unrelated in structure and function to products of Groups VI and VII and are not disclosed to capable of concurrent use, thus share no special technical feature.

Inventions of Groups I-V lack unity of invention with inventions of Groups VIII and IX because polynucleotide products of Groups I-V cannot be used in methods of Groups VIII and IX and the method of use of products required by Groups VIII and IX shares no special technical feature with the first method of use of products of Groups I-V.

Inventions of Groups I-V lack unity of invention with inventions of Groups X and XI because polynucleotide products of Groups I- V cannot be used in methods of Groups X and XI and the method of use of represen tational constructs required by Groups IX and X shares no special technical feature with the first method of use of products of Groups I -V.

Inventions of Group VI and Group VII lack unity of invention, one with the other, because each is disclosed to have a special technical feature defined by a capacity to bind a different structure and neither is disclosed to be capable of concurrent use with the other.

Inventions of Groups VI and VII lack unity of invention with inventions of Groups VIII and IX because the products of Groups VI and VII are not disclosed to be capable of use in the methods of Groups VIII and IX, thus can share no special technical feature.

Inventions of Groups VI and VII lack unity of invention with inventions of Groups X and XI because the products of Groups VI and VII cannot be used in methods of Groups X and XI, thus can share no special technical feature.

Inventions of Group VIII and Group IX lack unity of invention, one with the other, because the assay method of treatment of Group VII is not disclosed to be capable of concurrent practice with the assay method of Group IX, thus the separate assays can share no special technical feature.

Inventions of Groups VIII and IX lack unity of invention with inventions of Groups X and XI because the assays of Groups VIII and IX cannot be used in the representational methods of Groups X and XI, thus can share no special technical feature.

Inventions of Group X and Group XI lack unity of invention, one with the other, because the model required for the representational method of treatment of Group X cannot be the model utilized in the representational method of Group XI, and vice versa, thus the separate methods of inhibitor design can share no special technical feature.

Because these inventions lack unity and are distinct for the reasons given above, and have acquired a separate status in the art as shown by their different classifications, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR §1.48(b) and by the fee required under 37 CFR §1.17(h).

During a telephone conversation with Mr. Joseph R. Baker on August 13, 2001, a provisional election was made with traverse to prosecute the invention of Group II, claims 15-18, 21-23 and 25, wherein a specific verbal traversal was made of the requirement for restriction as between Groups II and IV, where both comprise the same set of claims. Inventions of Groups II and IV are examined herein to the extent they describe nucleic acid molecules that either comprise the nucleic acid sequence set forth in SEQ ID NO:2 or encode the same polypeptide, and nucleic acid molecules comprising portions of such nucieic acid molecules related to SEQ ID NO:2 that specify polypeptides comprising discrete domains of the encoded polypeptide of SEQ ID NO:4, as well as the encoded polypeptide of SEQ ID NO:4 and polypeptides comprising discrete domains thereof. Applicant must affirm this election in replying to this Office action. Claims 19, 20, 24 and 26-29 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

Claim 22 is objected to because of the following informalities: The claim lacks a period at the end of the claim sentence. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 15-18, 21-23 and 25 are rejected under 35 U.S.C. §101 because the claimed invention lacks patentable utility.

A claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility. It is agreed that SEQ ID NO:2 encodes a metalloprotease comprising a disintegrin domain. The specification states no specific *in vitro* utility for an isolated, integral SVPH3-17 metalloprotease, nor does it indicate a specific *in vitro* utility that is also substantial for a nucleic acid encoding the SVPH3-17 metalloprotease. The specification indicates, at page 5, that SEQ ID NO:2 and portions thereof may be used to identify other proteinase-encoding genes, to identify human chromosome 2, to map unspecified genes elsewhere on the chromosome, and to identify genes on chromosome 2 that are associated with

unspecified conditions. It is agreed that that SEQ ID NO:2 will identify chromosome 2 and other metalloproteinase-encoding genes but these are not considered to be substantial utilities because many other, unrelated, nucleic acid sequences will also identify metalloproteinase-encoding genes and human chromosome 2. Neither a specific nor substantial utility is seen in proposed uses of SEQ ID NO:2 in mapping unspecified genes elsewhere on human chromosome 2 or in identifying genes on chromosome 2 associated with unspecified conditions because many other, unrelated, nucleic acid sequences will serve these same purposes and no further genes or conditions are disclosed or suggested.

The specification indicates, at page 6, the encoded SVPH3-17 may be used "to study cellular processes such as immune regulation, cell proliferation, cell death, cell- to-cell interaction, and inflammatory responses." A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). While any one of the many cellular processes is a substantial occurrence, mere allegations of a prospective, potential, utility cannot rise to the level of a **credible** assertion of a **specific** *in vivo* utility that is substantial. Indeed, the specification's diffuse assertions indicate the contrary, that Applicant knew no specific utility for the claimed invention at the time the application was filed that would permit an immediate, specific, use by the public of a nucleic acid that encodes a SVPH3-17 metalloprotease or the metalloprotease itself.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 21-23 and 25 are also rejected under 35 U.S.C. §112, first paragraph. Specifically, since the claimed invention is not supported by either a **specific** asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 21-23 and 25 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

One species of clause (a), a genus of clause (b), a genus of clause (c), the species of clause (d), a genus of clause (e), two of the four minimal genera of clause (f), and the diverse genera of clause (g) are not examined pursuant to Applicant's provisional election of Inventions of Groups II and IV on August 13, 2001. The following subject matters are not subject to this rejection for lack of an adequate written description: the nucleic acid sequence species of clause (a) which is set forth in SEQ ID NO:2 and the two genera of nucleic acid sequences of clauses (b) and (e) which comprise those nucleic acid sequences isocoding with SEQ ID NO:2, as well as one of the genera of clause (f) which comprises nucleic acid molecules encoding fragments of SEQ ID NO:4 that exhibit at least disintegrin activity. Because the demonstration of disintegrin activity requires only cell membranes as substrates, Applicant is considered to have been in constructive possession of the invention described by these certain species, and genera, at the time the invention was made.

The specification fails to exemplify or describe, however, the preparation of subject matters of the products of clauses (c), (f), where a fragment exhibits proteinase activity, or a product of clause (h) of claim 15, or the products of clauses (a)-(j) of claim 25. Claims

16-18 and 21-23 are included in this rejection where, through dependency, they incorporate subject matters of clauses (c), (f), and (h) of claim 15. The specification fails to exemplify or describe the design, preparation or identification in Nature of the subject matters of clauses (c) and (h) of claim 15 which may encode polypeptides that either generally diverge from the overall amino acid sequence of SEQ ID NO:4 or diverge regionally from the amino acid sequence of SEQ ID NO:4. This is because there is no indication in the specification where the amino acid sequence might diverge, how it might diverge, or even what internal region might diverge, from the amino acid sequence of SEQ ID NO:4, or how an encoding nucleic acid sequence might correspondingly diverge in the codons that specify that amino acid sequence. Similarly, the specification fails to exemplify or describe the design, preparation or identification in Nature of the subject matters of clauses (a)-(h) and (j) of claim 25 which are "SVPH3-17polypeptides", yet differ somehow, whether generally or regionally, from the disclosed SVPH3-17 metalloprotease having the amino acid sequence of SEQ ID NO:4. The specification fails to disclose or to suggest other polypeptides that might be, for example, allelic variants or splice variants of the SVPH3-17 polypeptide of SEQ ID NO:4.

Neither does the specification exemplify the design, preparation or identification in Nature of fragmentary subject matters of clause (f) of claim 15 and clause (i) of claim 25 where such a fragment exhibits proteinase activity because the specification describes no substrate for the metalloprotease, thus neither Applicant, the artisan, nor the public can determine the nature of a fragment of claim (f) that exhibits proteinase activity. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Where the 10% of permitted

nucleic acid sequence deviations occur in first codon positions, clause (c) of claim 15 reaches nucleic acid sequences that encode generic proteins differing at as many as 30% of the positions in the amino acid sequence of SEQ ID NO:4, should they have the same length, and clause (h) of claim 25 permits 20% divergence in an amino acid sequence, the specification provides not even a suggestion as to where the first alteration in amino acid sequence should occur. Neither the claims nor the specification describe where the differences occur nor what the differences might be and the specification nowhere furnishes relevant identifying characteristics of a protein that comprises a peptide of clause (h) of claim 15 or peptides of clauses (a)-(g) of claim 25 but lacks the rest of SEQ ID NO:4, nor does it provide any characteristic permitting a correlation between undisclosed structures of any protein among the myriad species of generic proteins proposed in claims 15 and 25 and the disclosed amino acid sequence of SEQ ID NO:4.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such "relevant identifying characteristic[s]" that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Indeed, the claims rejected herein are, like the claims invalidated by the appellate panel in *University of California v. Eli Lilly*, designed to embrace other, as yet unknown, human metalloprotease-disintegrins and metalloprotease-disintegrins of other mammalian species as evidenced by the prior art made of record herewith. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of a nucleic acid sequence encoding any of these undisclosed generic proteins to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai*

Pharmaceutical Co., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the claimed products.

Claims 15-18, 21-23 and 25 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for preparation of nucleic acid sequences encoding a SVPH3-17 metalloprotease of SEQ ID NO:4, the preparation of a SVPH3-17 metalloprotease **having** the amino acid sequence set forth in SEQ ID NO:4, and the preparation of nucleic acid sequences encoding fragments of SEQ ID NO:4 having disintegrin activity and such an encoded fragment of SEQ ID NO:4,

does not reasonably provide enablement for preparation of nucleic acid sequences encoding a polypeptide having an amino acid sequence that diverges, by virtue of amino acid substitutions, deletions and insertions, or combinations thereof at as many as 30% of the amino acid positions from that of SEQ ID NO:4, the preparation of nucleic acid sequences encoding fragments of SEQ ID NO:4 having metalloprotease activity and the corresponding encoded fragments, for the preparation of nucleic acid sequences encoding undisclosed polypeptides comprising the seven peptide regions of SEQ ID NO:4 described in clause (h) of claim 15, or for preparation of amino acid sequences encoding polypeptides of clauses (h) and (i) of claim 15 or an undisclosed polypeptide of clauses (a)-(g) of claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

One species of clause (a), one genus of clause (b), one genus of clause (c), clause (d), one genus of clause (e), two of the four minimal genera of clause (f), and clause (g) are not examined pursuant to Applicant's provisional election of Inventions of Groups II and IV on August 13, 2001. The remaining species of clause (a), which is the nucleic acid sequence set forth in SEQ ID NO:2, and the remaining genera of clauses (b) and (e), which are nucleic acid sequences comprising nucleic acid sequences isocoding with SEQ ID NO:2, and the remaining minimal genera of clause (f), nucleic acid molecules that may encode only fragments of SEQ ID NO:4 that exhibit at least disintegrin or proteina se activity, are not subject to this rejection for lack of enablement as to making and use.

Claims 15 and 25 contemplate nucleic acid sequences encoding polypeptides, and the encoded polypeptides, having an arbitrary assignment of any or all possible amino acid substitutions, additions or deletions in a protease comprised by a claimed composition in as

many as 20% - in claim 25 – or 30% - in claim 15 – of the amino acid positions in the primary structure of SEQ ID NO:4. This rejection is stated under the first paragraph of the statute because the specification cannot support such degrees of amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the SVPH3-17 metalloprotease amino acid sequence set forth in SEQ ID NO:4. Claims 16-18 and 21-23 are included in this rejection because they depend from claim 15, thus incorporate its deficiencies in enablement as to making and use.

Indeed, neither the prior art made of record herewith nor Applicant's specification can identify, taken together, the 250 amino acids suggested by clause (c) of claim 15 in the amino acid sequence of the SVPH3-17 metalloprotease set forth in SEQ ID NO:4 that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to function as a metalloprotease. It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors used to analyze enablement). Mere sequence perturbation will not enable the design and preparation of nucleotide sequences encoding a myriad of divergent proteases and provide the public with a nucleotide sequence encoding a protease that retains its native function and the standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*,

427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); see also, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure only of a single B-cell growth factor allele). The Federal Circuit approved this standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

The Federal Circuit has also considered whether definitional statements might enable a claim scope argued to extend beyond a disclosed gene product having its native amino acid sequence to embrace a specific variant gene product encoded by a specifically-altered DNA sequence. *Genentech, Inc. v. The Wellcome Found. Ltd.*, 29 F.3d 1555, 31 USPQ2d 1161 (Fed. Cir. 1994). The court held that only a narrow structural and functional definition was enabling precisely because the sweeping definitions of scope in the patent specification could not reasonably have been relied upon by the PTO in issuing the patent. *Genentech*, 29 F.3d 15 at 1564-65, 31 USPQ2d at 1168. Applying the "*Forman*" factors discussed in *Wands*, ***supra***, to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for altering DNA sequences coding for, and encoded amino acid sequence of the SVPH3-17 metalloprotease set forth in SEQ ID NO:4, the to the extent recited in the claims,

b) the specification lacks working examples wherein the amino acid sequence of the SVPH3-17 metalloprotease or an SVPH3-17 metalloprotease-encoding nucleic acid sequence, are altered to the extent recited in the claims,

c) in view of the prior art publications of record herein, the state of the art a nd level of skill in the art do not support such alteration, and,

d) unpredictability exists in the art where no other metalloprotease-disintegrin of the class represented by the amino acid sequence of SEQ ID NO:4 has had as many as 250 amino acids specifically identified for concurrent modification.

Thus the present specification cannot be considered to support the scope of subject matters embraced by claims 15 and 25, even when taken in combination with teachings

available in the prior art. Limitation of the subject matters as indicated in the statement at page 10, lines 4-8, above is required in order to overcome this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15, 22 and 25 are rejected under 35 U.S.C. §112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention.

Claim 15 is ambiguous, therefore indefinite, in describing the same subject matter – "a nucleic acid molecule encoding an amino acid sequence comprising the sequence of . . . SEQ ID NO:4" – twice in clauses (b) and (e). That this subject matter is described in the alternative in both clauses does not save it from ambiguity because the two clauses may be construed as four separate clauses, two of which would then be identical. If the subject matter is described once in a claim, the artisan, and the public reading the claim, cannot know Applicant's intent in then describing it again in the same claim. This aspect of the rejection may be overcome by deleting the phrase "SEQ ID NO:4 or" from clause (e) of claim 15. Claim 22 is indefinite because it is incomplete in its description of a proposed method of "production". The terminal clause is non-specific where "culturing a host cell . . . under conditions promoting expression" need have nothing to do with expression of the SVPH3-17 polypeptide. Amending the claim to require specific expression of the SVPH3-17 polypeptide will overcome this aspect of the rejection. Even if the terminal clause were amended to specifically require expression of the SVPH3-17 polypeptide, the resulting method would not be a method of "production" but a method of expression of the SVPH3-17 polypeptide because the polypeptide would remain in the cell, unavailable. If Applicant wishes claim 22 to describe a method of "production", amending the claim to incorporate the description of claim 23 as second step would overcome this aspect of the rejection. However, a claim to a method of expression may independently be presented.

Claim 25 is indefinite because the preamble taken together with clauses (a)-(j) are susceptible of different constructions where clauses (a)-(g) might be considered to describe SEQ ID NO:4 or one or more undisclosed amino acid sequences that diverge from that of the disclosed SVPH3-17 at amino acid sequence regions beyond those described by clauses (a)-(j). How these divergent polypeptides might also be SVPH3-17 "polypeptides" is uncertain. Clause (h) compounds this ambiguity where the artisan, and the public seeking to interpret the claim, cannot know whether the 20% sequence divergence resides entirely within the region described by clauses (a)-(g), whether a 20% sequence divergence occurs entirely within the undefined regions outside the described regions, in which case there is a 20% divergence from the unknown, or whether the 20% sequence divergence resides in both the described regions of clauses (a)-(g) and the other, undefined, regions of the "polypeptide", effecting a divergence from the known and unknown amino acid sequences. Clauses (i) and (j) present different ambiguities because the preamble must be construed to describe an integral SVPH3-17 "polypeptide" which cannot simultaneously be only a "fragment" of itself having either, or even both, of the suggested activities. The first step in addressing this aspect of the rejection would be describing the nature of a "polypeptide" in the claim preamble that has only partial, regional, identities with the disclosed amino acid sequence of the SVPH3-17 metalloprotease of SEQ ID NO:4.

Allowable Subject Matter

While the elected claims are rejected above under 35 U.S.C. §§101 and 112, first paragraph, and claims 15, 22 and 25 are rejected under the second paragraph of 35 U.S.C. §112, the subject matters of clauses (a), (b) and (e) of claim 15 describing nucleic acid sequences comprising nucleic acid sequences identical to, or isocoding with, SEQ ID NO:2, as well as genera of clauses (f) and (h) which are nucleic acid sequences encoding a disintegrin region of SEQ ID NO:4 – a region comprising at least amino acid positions

496-599 of SEQ ID NO:4 – are free of the above rejections and are free of the prior art of record as well. In addition, genera of clauses (f) and (h) that comprise nucleic acid sequences encoding other, distinct regions of SEQ ID NO:4 - regions comprising at least amino acid positions 287-495 of SEQ ID NO:4 and those regions which constitute amino acid positions 1-58, 59-286, 287-495, 600-786, 787-817 and 818-832 of SEQ ID NO:4 - are also free of the prior art of record. Thus establishing a specific utility for these further subject matters that are free of the enablement and inadequate written description rejections stated above under 35 U.S.C. §112, first paragraph, would permit allowance of claims describing subject matters defined by the limitations of these clauses.

Publications of the MDC3-encoding cDNA of Sagane et al., 1998, made of record with Applicant's Information Disclosure and present in Japanese Patent No. 11/155,574, made of record herewith, as well as publication by Sheppard et al. in WO 00/02912 of a zdint1-encoding cDNA, made of record herewith, each of which is identical to SEQ ID NO:2 herein, are not in the prior art because they were made after Applicant's February 11, 1998, priority date. SEQ ID NO:4 of the 5,552,526, 5,631,351 and 5,701,341 published in patents to Nakamura et al., made of record herewith, and in EP 0 633 268 and by Katagiri et al., 1995, both made of record with Applicant's Information Disclosure Statement, fails to rise to the level of prior art because this closest of the coding sequences of Nakamura et al. is but 57.5% similar over 84% of the length of the region encoding the amino acid sequence of SEQ ID NO:4 herein, thus has less than 49% similarity to the coding capacity of SEQ ID NO:2 while clause (c) of claim 15 requires that even a degenerate nucleic acid sequence molecule that hybridizes to a nucleic acid sequence of clause (b) isocoding with SEQ ID NO:2 be 90% identical to the degenerate sequence over its entire length. Similarly, the MDC2α- and MDCβ-encoding cDNAs of the 1998 disclosed by Sagane et al., 1998, made of record with Applicant's Information Disclosure

Statement, and the ADAM12-encoding cDNA disclosed by Gilpin et al., 1998, made of record herewith are too distant in sequence identity to a full-length generic sequence encoding SEQ ID NO:4 to meet limitations of clause (c) of claim 15. Although each has a high degree of sequence identity with SEQ ID NO:2 herein, the human DNA sequences of 526-nucleotides having EMBL-GenBank database Accession Nos. AA050162 and W75581, made of record with Applicant's Information Disclosure Statement, and the further murine and human DNA sequences having EMBL-GenBank database Accession Nos. AA718688, F08148, AA511039 and R52569, made of record herewith, likewise fail to meet limitations of clause (c) of claim 15 because they are too limited in coding capacity to approach 90% identity with a degenerate sequence encoding SEQ ID NO:4.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached from 8:00AM-6:30PM EST on Mondays, Wednesdays, and Fridays and from 11:30AM-6:00PM EST on Tuesdays and Thursdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

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February 25, 2002

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